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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/949,904	10/15/1997	EDWARD R. LAVALLIE	GI-5288B	8744

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EXAMINER	
UNGAR, SUSAN NMN	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/949,904	LAVALLIE ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *12 May 2004 and 12 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-19,21-24,26 and 27* is/are pending in the application.

4a) Of the above claim(s) *1-17, 21, 24, 26, 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *18,19,22,23 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *April 14, 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The Amendment filed May 12, 2004 in response to the Office Action of November 12, 2003 is acknowledged and has been entered. Claims 18-19, 22-23, 33 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC 101

3. Claims 18-19, 22, 23, 33 remain rejected under 35 USC 101 for the reasons previously set forth in the Paper Mailed November 12, 2003, Section 4, pages 2-7.

Applicant reiterates previous arguments drawn to Example 7, these arguments have been previously considered and not found persuasive for the reason of record.

Applicant submits a Declaration under 37 CFR 1.132 signed by Inventor LaVallie which Applicant believes is sufficient to establish utility. Applicant points to MPEP 2107.03, part VI wherein the MPEP states that Affidavit evidence from experts in the art indicating that there is a reasonable expectation of success, supported by sound reasoning, usually should be sufficient to establish that a utility is credible. In particular, (1) the LaVallie Declaration states that Mr. LaVallie has reviewed the Rosen et al reference in light of his own knowledge of the art relating to cell lines and *in vivo* activity. Mr. LaVallie states that Rosen asserts that the "response of the cells to ..... (BMP-2.....) is **likely** (emphasis added) to recapitulate the *in vivo* condition. Mr. LaVallie also points to a model of *in vivo* differentiation that the authors propose, based upon their observations with the MYC-clone 14 cells. Therefore, the authors believe (and we concur) that the *in vitro* responsiveness of these cells can reasonably mimic the *in vivo*

condition, (2) the increase in cartilage markers in Example 7 demonstrates that SDF-5, in combination with BMP-2, is involved in the regulatory pathway for the formation of cartilage and thus the present invention can be used in treatment of cartilage disorders such as osteoarthritis, rheumatoid arthritis and articular cartilage defects and the use of SDF-5 in combination with BMP-2 to increase cartilage formation is a credible utility.

The argument has been considered but has not been found persuasive because the (1') proposed model does not appear to have been validated for the effectiveness of novel molecules for *in vivo* treatment. Further a review of the literature using the STN:Bioscience Database Group which comprises greater than 64 databases, including both the US Patent Database as well as the US Published Application Database, does not reveal a single hit based on a search of MLB13MYC-clone 14 cells that would suggest that a direct nexus or correlation can be drawn between the *in vitro* responsiveness of these cells and effectiveness for treatment in the *in vivo* condition, (2') Example 7 is drawn to an increase in Collagen type II and IX, decorin and aggrecan mRNA and not to an increase in the proteins that are involved in the regulatory pathway for the formation of cartilage. Further, as previously set forth, although the decrease in hypertrophic cartilage and bone marker mRNA was found to be "significant", the specification clearly omits the term "significant" when discussing the increase of the mRNA compared to BMP-2 alone. Thus, it appears that the increase is not significant, even in the *in vitro* environment wherein the novel molecule is in contact with the cell-line model for the full treatment period. Further, the specification states that "there seems to be a greater enhancement of cartilage phenotype with the SDR-5 combination". Apparently the putative enhancement is so small that

applicant is not even sure that it is there. Given the information in the specification, given what was known in the art at the time the application was filed, it is clear that additional work must be done in order to determine if the present invention can be used as suggested by Mr. LaVallie, that is can be used in treatment of cartilage disorders such as osteoarthritis, rheumatoid arthritis and articular cartilage defects and the use of SDF-5 in combination with BMP-2 to increase cartilage formation. As set forth above, cartilage markers were not demonstrated to be increased, rather mRNA encoding said markers were shown to be increased and for the reasons of record, additional work must be done in order to determine how to use the claimed invention and the invention does not have substantial utility and therefore credible utility.

Inventor LaVallie further states that as one of skill in the art, he believes that the *in vitro* data as set forth in the instant specification reasonably supports applications *in vivo.*

The argument has been considered but has not been found persuasive for the reasons set forth previously and above.

Applicant argues that Examiner has used too strict a standard for utility and that there are no logical fallacies in the assertion that the increase in cartilage markers indicates an increase in cartilage formation and that this increase can be used to treat cartilage disorders and that an *in vivo* example is not required.

The argument has been considered but has not been found persuasive, even if it were to be found that information in the *in vitro* model could be directly extrapolated to treatment in the *in vivo* condition, even if there was

an increase in the protein levels of cartilage markers as a result of the interaction of BMP2 and SDF-5, the specification does not teach the levels of increase required for the use of the instant invention, does not teach that the levels of increase are sufficient to in fact alter cartilage formation compared to BMP-2 administration alone and certainly nothing in either the specification or in the art of record supports the use of the claimed increased to treat cartilage disorders and further work is required in order to use the claimed invention, thus the invention does not have substantial utility. Further, although Applicant is correct that an *in vivo* example is not required, it is clear that the claimed invention is an undeveloped art. The more that is known in the prior art about the nature of the invention, how to use the invention, the less information needs to explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention, the specification would need more detail about the nature of the invention and how to use the invention in order to support utility. For the reasons of record, since additional work is required to determine how to use the claimed invention, the invention does not have substantial utility. Since the invention is drawn to an undeveloped art, the invention does not have a well established utility. Since the invention has neither a well-established nor a substantial utility, the invention does not have a specific utility and credibility of utility cannot be evaluated.

Applicant argues that Examiner's interpretation of the Rosen reference in the Official Action is inaccurate and reinterprets the statements in the Rosen reference.

The argument has been considered but has not been found persuasive because Examiner's interpretation is reasonable for the reasons of record.

Applicant further argues that the Rosen model was used to obtain data that could not be extrapolated from an *in vivo* experiment and that Rosen et al state that these results correlate well with *in vivo* data on BMP activity.

The argument has been considered but has not been found persuasive because the data obtained was data that was drawn to teasing out the differentiation mechanisms of limb bud cells into cells of both the cartilage and bone lineages and suggest that BMP-2 is a potent regulator of skeletal cell differential. Since it was not possible to extrapolate this data from *in vivo* experiments, an *in vitro* cell model was developed. The fact that the BMP-2 data correlated with *in vivo* data on BMP activity suggests that the model is appropriate for examining the mechanism of BMP. It is noted that the correlation was only to the effects of BMP-2 on differentiation and the expression of chondrocyte markers and there was no suggestion that the model could be used to provide a nexus between *in vitro* experimentation and efficacy of *in vivo* treatment using BMP-2 in combination with novel molecules. Thus, it is not possible to determine, using this *in vitro* cell model, whether SDF-5 would have any effect on differentiation or expression of chondrocyte markers *in vivo* given the clear disclosure in Rosen et al that the cell culture environment is different than the *in vivo* environment, especially given the apparent less than significant increase in mRNA production.

Applicant points to the submitted Banerjee et al reference wherein the reference states that the MLB13MYC clone 14 represents an

undifferentiated early skeletal progenitor that differentiates into chondroblasts and then into osteoblasts in response to BMP-2, inferring that the model can be used to provide a nexus between effects in the *in vitro* system and in the *in vivo* environment and argues that a reliable correlation is not required but rather that a reasonable correlation is required.

The argument has been considered but has not been found persuasive because the model is again used, not to predict *in vivo* effects of an undeveloped molecule upon chondrocyte differentiation, but rather to tease apart the mechanism of early skeletal progenitor differentiation. Nowhere in Banerjee et al does the reference suggest that the model is effectively used to provide a nexus between *in vitro* assays and efficacy in treatment in the *in vivo* environment. Neither a reliable nor a reasonable correlation has been established.

Applicant argues that the MLB13MYC cell line is correlated with in vivo activity in that *in vitro* discoveries are a determinant in performing *in vivo* experiments and in particular, argues that the Gori et al reference teaches that "Because BIG-3 was expressed *in vitro* by cells of the osteoblastic lineage, we performed immunohistochemistry to determine whether osteoblasts express BIG-3 *in vivo*".

The argument has been considered but has not been found persuasive and Applicant validates Examiner's argument drawn to substantial utility. Clearly additional work must be done in order to determine whether the apparently insignificant synergistic increase in cartilage marker mRNA, upon treatment of a cell line with BMP-2 and SDF-5, can in fact be used to

treat cartilage diseases as taught by the specification and suggested by Applicant.

Applicant states that Rosen teaches the function of morphogens in the *in vivo* process of expression of chondroblast-like phenotype. The statement is acknowledged but is not found persuasive, for the reasons of record, it has not been established that SDF-5 is a morphogen and the utility being argued at this time is drawn to treatment of cartilage diseases, not to the expression of chondroblast-like phenotype.

Applicant argues that, given the synergy of SDF-5 and BMP-2, SDF-5 in conjunction with BMP-2 performs a regulatory role in the formation of cartilage.

The argument has been considered but has not been found persuasive for the reasons set forth previously and above.

Applicant discloses the findings in *Cross v. Itzuka*, wherein based on the *in vitro* and *in vivo* testing of parent compounds, derivatives were only tested *in vitro* and the court found that *in vitro* testing was sufficient to provide utility for the claims and Applicant argues that this demonstrates that there is a reasonable correlation between *in vitro* and *in vivo* tests.

The argument has been considered but has not been found persuasive because the fact patterns in *Cross v. Itzuka* and the instant invention are not the same. In particular, the synergistic efficacy of SDK-5 with BMP-2 has not been demonstrated *in vivo*, and the invention is not drawn to derivatives of a known, successful molecule.

Applicant argues that MPEP 2107.01 exemplifies a real world use as both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have substantial utility define a real world use and points to the cite in the specification wherein the specification states that the claimed invention can be used in the treatment of cartilage disorders and the examples in the MPEP in no way resemble the current situation since the application describes the properties of the claimed product, asserts the use of the invention and specifies the diseases which can be treated.

The argument has been considered but has not been found persuasive for the reasons set forth previously and above the claimed invention does not have any of substantial, well-established, specific utility drawn to the treatment of cartilage diseases for the reasons of record.

Applicant states that another suggested utility of the instant invention that has not been previously mentioned is the use of the invention to obtain chondrocytes and cartilage tissue from the *in vitro* experiment to be administered to a patient. The suggestion has been considered but has not been found persuasive because it has not been determined whether the apparently insignificant increase of mRNA cartilage tissue markers seen upon treatment of cells in culture with BMP-2 and SDF-5 has any effect on the production of chrondrocytes or cartilage tissue *in vitro* and additional work is required in order to make that determination, thus the invention does not have substantial utility.

Applicant suggests that SDF-5 could be used to treat embryonic stem cell lines to cause the formation of cartilage tissue as disclosed in the

prophetic Example 8. The suggestion has been considered but has not been found persuasive because the specification as originally filed does not contemplate this utility and for the reasons set forth previously and above, additional work is required in order to determine the effects of the SDF-5 proteins on embryonic stem cells.

The arguments have been considered but have not been found persuasive and the rejection is maintained.

Finally, as clearly set forth in the paper mailed March 26, 2002, section 8 pages 4-11, the specification is replete with speculations as to the utility of the claimed inventions, the specification is replete with phrases such as "may include the ability to regulate the binding of Wnt proteins", "may include the ability to regulate the formation, differentiation, proliferation and/or maintenance of cells and/or tissues", "may include the ability to enhance and/or inhibit the formation, growth, proliferation, differentiation and/or maintenance of chondrocytes and/or cartilage tissue" (see page 5, lines 7-17), may be utilized to enhance and/or inhibit the formation, growth proliferation, differentiation and/or maintenance of beta cells and other cell types". The specification speculates that compositions comprising the claimed invention may be employed in methods for treating tissue defects, and maintenance of various types of tissues including epidermis, nerve, muscle, connective tissue, bone, tendon, ligament and other tissues and speculates that the compositions may be used to prevent rheumatoid arthritis, oseteoarthritis and other abnormalities of cartilaginous or other organs and tissues (see para bridging pages 7-8). The specification states that the claimed invention has potential signal transduction regulation

activities (see page 11, lines 12-24). The specification continues to speculate as to other possible useful properties for the claimed invention including angiogenic, chemotactic and or chemoattractant properties, induction of formation of cells capable of secreting valuable hormones (see page 20, lines 11-19) and states that the proteins of the invention are expected to exhibit one or more of a laundry list of activities (see pages 23, 24, 26, 32, 33, 356, 38-41). The issue raised in the utility rejection imposed in the paper mailed March 26, 2002 is that at the time the invention was made, the claimed invention did not have a substantial, well-established, specific utility. This is clearly demonstrated by the speculatory language in the specification. Thus with the terms "may enhance", "may inhibit", "may regulate", "may be used in treating", "may prevent", "potential signal transduction regulation activities", "expected to exhibit", the specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed invention. Applicant has cited numerous examples of case-law to establish that the claimed invention has utility. It is noted that Applicant has neglected to cite *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966), wherein the court expressed the opinion that an invention must have either an immediately apparent or fully disclosed real world utility. The court held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. . . . a patent is not a hunting license. . . .[i]t is not a reward for the search, but compensation for its successful conclusion.

The instant claims are drawn to an invention of unknown biological significance at the time the invention was made. There is no evidence of record or any line of reasoning that would support a conclusion that the claimed invention, as of the filing date, was useful for any of the speculated purposes. Until some actual and specific significance can be attributed to the claimed invention one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use the claimed invention. Thus there was no immediately apparent or "real world" utility as of the filing date. Applicant's reiteration of previous arguments, Applicant's citation of case law has not been found persuasive for the reasons set forth previously and above.

Claim Rejections - 35 USC 112

4. Claims 18-19, 22, 23, 33 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in the paper mailed November 12, 2003, Section 5, pages 7-11.

Applicant reiterates arguments drawn to the Dermer article being one editorial opinion. The argument has been considered but has not been found persuasive for the reasons of record.

Applicant further argues that the situation described in Dermer is different from the invention in that it has been well established that the *in vitro* cell line correlates well with *in vivo* models.

The argument has been considered but has not been found persuasive since it has not been established that the *in vitro* cell line is correlative for

the instantly suggested utility of the claimed invention or for the treatment of any disease.

Applicant argues that it is not necessary for the clone 14 cell line to be identical to the source from which it was derived and points once again to *Cross v. Iizuka* wherein *in vitro* results are generally predictive of *in vivo* test results and that this was considered enough to prove utility.

The argument has been considered but has not been found persuasive because as set forth above, the fact pattern in the instant application is not the same as the fact pattern in *Cross v. Iizuka* and therefore the findings therein are not relevant to the instant application.

Applicant argues that *in vitro* models are considered a determinant for successful *in vivo* experiments and again cites Gori.

The argument has been considered but has not been found persuasive for the reasons set forth previously and above.

5. No claims allowed.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R., 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvette Eyler, can be reached at 571-272-0871 The fax phone number for this Art Unit is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
July 15, 2004